Phone: (412) 562-2400

L-6

United Steelworkers of America
AFL-CIO-CLC
FIVE GATEWAY CENTER, PITTSBURGH, PA. 15222

September 16, 1982

Mr. Tom Hall
OSHA Division of Consumer Affairs
U.S. Department of Labor, Room N-3635
3rd Street & Constitution Avenue, N.W.
Washington, DC 20210

Dear Mr. Hall:

Re: Docket H-022

On August 31, 1982, the USWA submitted a large packet of post-hearing evidence to the record of OSHA's rulemaking on "hazards communication." Since that time, we have received several additional documents which we believe the Agency could find useful in its deliberations. Therefore, we are taking the liberty of submitting them in quadruplicate to the record. We stress that these documents were received by us only after the September 1 deadline. They are:

1. Vainio; "Inhalation anesthetics, anticancer drugs and sterilants as chemical hazards in hospitals;" Scand j work environ health; Vol. 8, pp. 94-107 (1982).

2. A DuPont material safety data sheet on formaldehyde. We received this from a chemical distributor on September 10 of this year, although we had requested it several months earlier. You will note that it does not contain any indication that formaldehyde is a carcinogen (although it does note that the carcinogen bis-chloromethyl ether can be formed if formaldehyde is mixed with hydrochloric acid). We do not yet know whether the material safety data sheet is out of date, or whether it reflects DuPont's current thinking on formaldehyde, but we suspect the first explanation is more accurate, since the attachment to the MSDS is dated 7/79. In either event, this MSDS communicates inadequate information and demonstrates the need for unambiguous hazard determinations, frequent updating, and coverage of chemical distributors in addition to chemical manufacturers.

Sincerely yours,

Mike Wright

Mike Wright
Industrial Hygienist
Safety and Health Department

MW/ccz

cc: Adolph E. Schwartz
Mary-Win O'Brien
Peg Seminario

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DUPONT

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MATERIAL SAFETY DATA SHEET

IDENTIFICATION

Name Formaldehyde Solutions USP 37-7, 37-11; LM 37-52%

Synonyms Formalin, Methanal

Chemical Family Aldehyde

CAS Name Formaldehyde

CAS Registry No. 50-00-0

I.D. Nos./Codes NIOSH Registry No. LP 89250
Wiswesser Line Notation VHH

Manufacturer/Distributor
E. I. du Pont de Nemours & Co., (Inc.)

Address
Wilmington, DE 19898

Product Information and Emergency Phone
(302) 774-2421

Transportation Emergency Phone
(800) 424-9300

HAZARDOUS COMPONENTS

Material(s)	Approximate %		
USP 37-7	Formaldehyde	37%	Methanol 7%
USP 37-11	"	37%	" 11%
LM Grades	"	37-52%	" 0.9-1.3%

PHYSICAL DATA

Boiling Point, 760 mm Hg 96.7-99.7°C (206-211.5°F)

Melting Point Polymerizes & separates below 10-51°C

Specific Gravity 1.085-1.13

Vapor Pressure@ 25°C=17-20mm Hg; @ 37.7°C=39-42mm

Vapor Density ~1

Solubility in H_2O 100%

% Volatiles by Vol. 100%

Evaporation Rate (Butyl Acetate = 1) ~1.8

Form Liquid Appearance Clear

Color Colorless Odor Pungent

pH Information 2.8-4.0

Octanol/Water Partition Coefficient Log P = 0

FIRE AND EXPLOSION DATA

Flash Point 60-83°C Method TCC

Autoignition Temperature 424°C, 795°F

Flammable Limits in Air, % by Vol. Lower 7 Upper 73

Fire and Explosion Hazards Combustible

Extinguishing Media Water, "Alcohol" foam, dry chemical, carbon dioxide

Special Fire Fighting Instructions Wear self-contained breathing apparatus. Cool container with water spray.

HAZARDOUS REACTIVITY

Instability Reacts with many compounds. Reaction with phenol, strong acids, or alkalies may b violent.

Incompatibility Reaction with hydrochloric acid may form bis-chloromethyl ether, an OSHA regulated carcinogen.

Decomposition Slow, at elevated temperatures. Releases formaldehyde gas.

Polymerization Non-hazardous polymerization may occur.

HEALTH HAZARD INFORMATION

Exposure Limits OSHA 8 hour Time Weighted Average, TWA = 3 ppm; Ceiling = 5 ppm
ACGIH TLV = 2 ppm (Ceiling)

Routes of Exposure and Effects Causes eye burns; effects may be delayed. Harmful if inhaled or absorbed through skin. May cause allergic skin reaction. USP grades may be fatal or cause blindness if swallowed; cannot be made non-poisonous.

First Aid SEE FORMALDEHYDE ATTACHMENT

PROTECTION INFORMATION

Ventilation Maintain adequate ventilation.

Personal Protective Equipment Coverall chemical safety goggles, rubber gloves, boots or overshoes.

Other

DISPOSAL PROCEDURES

Aquatic Toxicity TLm 96:100-10 ppm

Spill, Leak or Release SEE FORMALDEHYDE ATTACHMENT

Waste Disposal

SHIPPING PRECAUTIONS

Transportation

Shipping Containers SEE FORMALDEHYDE ATTACHMENT

Storage Conditions

REFERENCES AND ADDITIONAL INFORMATION

Do not get in eyes. Avoid breathing vapor, mist. Avoid contact with skin or clothing. Wash thoroughly after handling. Wash contaminated clothing thoroughly before reuse.
For more information refer to: Du Pont Formaldehyde Data Sheet
Du Pont Formaldehyde Properties, Uses, Storage & Handling Bulletin.

DUPONT

FORMALDEHYDE ATTACHMENT

HEALTH HAZARD INFORMATION

First Aid

In case of eye contact, call a physician. Immediately flush eyes with plenty of water for at least 15 minutes. In case of skin contact, immediately wash skin with soap and water and flush with plenty of water for at least 15 minutes. If inhaled, remove to fresh air. If not breathing, give artificial respiration, preferably mouth to mouth. If breathing is difficult, give oxygen. Call a physician. If swallowed, induce vomiting immediately by giving 2 glasses of water and sticking finger down throat. Call a physician. Never give anything by mouth to an unconscious person.

DISPOSAL PROCEDURES

Aquatic Toxicity

TLm 96: 100-10 ppm

Spill Leak or Release

Keep upwind of leak; evacuate area until gas has dispersed. Soak up small leaks with rags and dispose of in covered metal containers. Dike large spills. Neutralize with dilute (<5%) solutions of ammonia, sodium sulfite or sodium bisulfite. Flush with plenty of water.

Waste Disposal

Comply with Federal, State & Local regulations. If approved, flush to chemical sewer, incinerate, dispose in sanitary landfill, or flush to waste water treatment system. Dilute solutions will be handled by biochemical action in formaldehyde adapted waste treatment systems; water spray or fog will help absorb escaping fumes. See 40 CFR 116.

SHIPPING PRECAUTIONS

Transportation

DOT Shipping name - Formaldehyde or Formalin solution. DOT Hazard Class = Combustible liquid (in containers over 110 gallons); ORM-A (in containers of 110 gallons or less). STCC Code = 281 8141. UN No. 1198.

Shipping Containers

Railroad tank cars, tank trucks, drums.

Storage Conditions

Keep container closed, Keep away from heat and open flame. Store in tested tank or warm room, above minimum storage temperature for grade handled.

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Scand j work environ health 8 (1982) 94—107

Inhalation anesthetics, anticancer drugs and sterilants as chemical hazards in hospitals

by Harri Vainio, MD[1]

VAINIO H. Inhalation anesthetics, anticancer drugs and sterilants as chemical hazards in hospitals. *Scand j work environ health* 8 (1982) 94—107. In recent years, there has been a considerable increase in the use of chemicals (chemical sterilants and antimicrobial agents, antineoplastic drugs, and anesthetic gases) in hospitals. The possible existence of occupational health hazards has often been overlooked in light of the great advantages provided by the use of chemical agents. It appears that certain hospital sectors, such as anesthesia units, sterilizing units and oncology units, require different degrees of caution and protective measures with respect to the handling of chemicals. The scientific evidence on which recommendations should be based is, in most cases, fairly meager; until more is known about the hazards, it would be prudent to minimize the occupational exposure to chemicals in hospitals.

Key terms: carcinogenicity, ethylene oxide, formaldehyde, halothane, hexachlorophene, mutagenicity, nitrous oxide, reproductive hazards, spontaneous abortions.

Many chemical agents have been and are being used in hospitals as anesthetics, chemical sterilizers, drugs, cytostatic agents, etc. Some of these chemicals (particularly chemical sterilants and some cytostatic drugs) are highly reactive chemically. Others, such as anesthetic gases, act on lipid membranes. Until recently, little thought has been given to the possible adverse health effects of occupational exposure to chemicals in hospitals. This review examines the occupational health hazards of the types of chemicals most frequently used in hospital facilities.

INHALATION ANESTHETICS

Properties and occurrence

Inhalation anesthesia was first introduced in 1842. Since then, many different chemicals have been used as inhalation anesthetic agents. Although the possible health hazards of occupational exposure to anesthetic agents have only recently aroused interest [see the reports of Edling (22) and the National Institute for Occupational Safety and Health (65)], more attention has been paid to the physicochemical properties of such anesthetic agents.

At room temperature and room pressure inhalation anesthetics are either gases or volatile liquids. The only gas in widespread use is nitrous oxide. Other commonly used anesthetics are either halogenated ethanes or ethers. Diethyl ether, divinyl ether chloroform, trichloroethylene, and fluroxane are either flammable or considered so toxic that most countries have stopped using them.

The halogenation of aliphatic hydrocarbons decreases their volatility and flammability and, in some cases, increases their lipid solubility. Polyhalogenated compounds are also more stable than monohalogenated compounds.

The uptake and the clearance of inhalation anesthetics have recently been reviewed (29). The metabolism of these agents has been considered in another review (88).

Anesthetic agents have not only been found in the ambient air of operating rooms, but also in the ambient air of recovery rooms, delivery rooms, and dental

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surgery rooms [see Tolonen (84)]. The concentration of anesthetic waste gases and vapors depends on a variety of factors, including the method and technique of anesthesia and the specific scavanger operations done. The level of halothane frequently found in older operating rooms varies between 1 and 70 ppm, and the concentration of nitrous oxide frequently ranges from 400 to 3,000 ppm. In newer facilities with better systems of general ventilation, appreciably lower concentrations have been measured. But occasionally, some high peak exposures can occur, eg, during intubation or when a face mask is used.

Since the potential health hazards of inhalation anesthetics have been recently summarized (22, 65), I will not give an exhaustive literature review. However, I will discuss those adverse health hazards that are the most important from the point of view of occupational exposure.

Hazards to reproduction

The first hint that the personnel of operating rooms might be exposed to health hazards came from a Russian study by Vaisman (87). He had sent a questionnaire to 354 Russian anesthetists (of whom 28 % used halothane, 59 % nitrous oxide, and 98 % ether) and had analyzed 303 replies. The fact that only 7 of 31 pregnancies among these doctors were trouble-free stimulated researchers in other countries to carry out similar surveys. The main concerns of these studies have been spontaneous abortions and malformed children (tables 1 & 2).

The standard approach of each study has been to use a register to identify a group of exposed persons, who are then sent questionnaires inquiring about the past occurrence of the topics under study. These studies have provided reasonably convincing evidence of an increased risk of spontaneous abortion among exposed women (but not among the wives of exposed men).

A recent American study compared men dentists and women chairside assistants who used anesthetic gases (mainly nitrous oxide) with those who did not (15). The study showed a highly significant association between exposure to anesthetic gases and spontaneous abortions among the chairside assistants. The rate rose from 8.1 per 100 pregnancies among those not exposed to 19.1 per 100 pregnancies among those heavily exposed. Because the concentrations of anesthetic gases measured during dental surgery are several times higher than those found in general operating rooms, a survey of the pregnancies of dentists' wives could be expected to be more indicative of the effects of paternal exposure. Interestingly, an association has been observed for dentists' wives (6.7 per 100 for nonexposed husbands vs 10.2 per 100 for heavily exposed husbands). No increase in congenital malformations among the children of exposed dentists was observed.

In summary, it is reasonably conclusive that operating room staff have an increased risk of spontaneous abortion. The recent study of dentists and chairside assistants, together with evidence from experimental animals (56), suggests that high concentrations of nitrous oxide may be the causative factor.

Some studies, eg, those by Cohen et al (13), Knill-Jones et al (51), and Göthe et al (35), have reported that the children of women exposed to anesthetic gases during pregnancy have a higher risk of malformations. No increase in congenital malformations was observed among the children of dentists exposed to inhalation anesthetics (15), nor did a Swedish study of women operating room personnel find an increased occurrence of congenital malformations (25). The existing evidence for the increased risk of the birth of a malformed child is much weaker than the evidence for spontaneous abortion.

Carcinogenicity and mutagenicity

Some anesthetic agents are known to have mutagenic potential [see Baden & Simmon (3)]. Halothane, for instance, has been found to induce recessive lethal mutations in *Drosophila* (53). Halothane is also able to increase the level of nondisjunction in *Drosophila* (11). Furthermore, halothane has reactive intermediates that can bind covalently to cellular macromolecules (30) and are mutagenic in bacterial tests (32). It has also been reported that nitrous oxide, another commonly used anesthetic

gas, increases the number of recessive sex-linked lethal mutations in *Drosophila* (31).

Two retrospective epidemiologic studies have been published concerning the deaths of members of the American Society of Anesthesiologists during the intervals of 1947—1966 and 1967—1971 (5, 6). The study of the first period suggested that anesthetists were at an increased risk of death from tumors of the lymphatic and reticuloendothelial systems. No such difference was apparent in the later period. A third study, done in the United Kingdom, followed over 20,000 men doctors for up to 20 a (20). Some 1,250 of the doctors were full-time or part-time anesthetists. No excess of deaths from cancer was observed, although 5 deaths from cancer of the pancreas occurred, versus 1.7 expected, among the full-time anesthetists.

In another extensive American study, morbidity was followed in a questionnaire survey of 73,496 persons. This study found a higher frequency of cancer, especially

Table 1. Surveys on spontaneous abortion among exposed females and among wives of exposed males.

Subjects	Exposed group			Reference group			Reference
	Pregnancies (N)	Abortions N	Abortions %	Pregnancies (N)	Abortions N	Abortions %	
United Kingdom in 1972							
Doctors	737	133	18	2,150	323	15	Knill-Jones et al (51)
United Kingdom in 1975							
Doctors	523	84	16	7,296	803	11	Knill-Jones et al (50)
United States in 1971							
Nurses	36	11	28	34	3	9	Cohen et al (12)
Doctors	37	14	38	58	6	10	Cohen et al (12)
United States in 1974							
Nurses	1,826	310	17	1,948	292	15	Cohen et al (13)
Doctors	468	80	17	308	28	9	Corbett et al (17)
Finland in 1973							
Nurses	257	51	20	150	17	11	Rosenberg & Kirves (77)
United Kingdom in 1975							
Wives of exposed doctors	5,891	648	11	7,296	803	11	Knill-Jones et al (50)
United States in 1974							
Wives of exposed nurses	1,350	162	12	54	5	10	Cohen et al (13)
Wives of exposed doctors	3,416	410	12	1,982	258	13	Corbett et al (17)

Table 2. Major malformations in children of exposed females and wives of exposed males.

Subjects	Exposed group			Reference group			Reference
	Infants born (N)	Infants malformed N	Infants malformed %	Infants (N)	Infants malformed N	Infants malformed %	
United Kingdom in 1972							
Doctors	893	27	3	1,835	59	3.2	Knill-Jones et al (51)
United Kingdom in 1975							
Doctors	438	7	1.6	6,442	71	1.1	Knill-Jones et al (50)
United States in 1974							
Nurses	1,480	142	9.6	1,629	124	7.6	Cohen et al (13)
Doctors	384	23	5.9	276	8	3.0	Corbett et al (17)
Finland in 1973							
Nurses	207	0	0	133	0	0	Rosenberg & Kirves (77)
United Kingdom in 1975							
Wives of doctors	5,175	57	1.1	6,442	71	1.1	Knill-Jones et al (50)
United States in 1974							
Wives of nurses	1,168	96	8.2	49	2	3.7	Cohen et al (13)
Wives of doctors	2,988	161	5.4	1,714	72	4.2	Corbett et al (17)

leukemia and lymphoma (13), among the women exposed to anesthetic gases. No such higher frequency was found for the men with such exposure.

In conclusion, the evidence that inhalation anesthetic gases cause increased cancer risk among exposed persons is still fairly limited. Some of the anesthetic agents are, however, known to be active mutagenically in various test systems. Therefore, special attention should be paid to the epidemiologic surveillance of persons exposed to anesthetic agents.

Liver disease

Uncertainty about whether halothane causes hepatitis has led to much debate. Although halothane itself is not directly toxic to the liver, its metabolites fulfill the criteria for hepatotoxins (30). In many animal experiments hepatocellular damage has been reported after exposure to high doses of halothane and methoxyflurane (65), and also after long-term exposure to low doses of halothane, isoflurane, and diethyl ether (83). However, the only available data for man are the case reports of liver damage either among patients anesthesized with halothane or among anesthetists exposed to halothane [see, Edling (22)]. A few comprehensive epidemiologic studies have reported an increased frequency of liver disease among anesthesiologists (13, 14, 65, 82).

Renal damage

Methoxyflurane is known to cause renal tubular necrosis in experimental animals and man (16, 61, 65). The actual cause of renal damage may be the metabolites inorganic fluoride and oxalic acid. Increased fluoride concentrations in the urine of delivery ward and operating room personnel have been measured (18). One survey, done by Bruce et al (5), suggested an increased incidence of chronic renal disease as a cause of death among anesthetists.

At concentrations of 10 to 500 ppm halothane has caused morphologically detectable kidney damage in rats (9). Several volatile metabolites of halothane are nephrotoxic in mice (79).

Toxic effects in the central nervous system

Anesthetic agents are lipid-soluble narcotizing gases or solvents. Thus they also have the potential to cause chronic toxic effects in the central nervous system. Some of the recent evidence for the neurotoxicity of anesthetic agents has been given in a review by Edling (22). The central issue is an almost complete lack of studies on the chronic neurotoxic effects produced after many years of exposure to anesthetic gases.

The results of studies of the acute effects on the central nervous system are somewhat contradictory. Korttila et al (52) found no impairment in the driving skills of nurses after occupational exposure to halothane (0—43.7 ppm) and nitrous oxide (100—1,200 ppm). A Swedish study of 32 anesthetic nurses found a tendency towards poorer performance on psychological tests in a high exposure group (41). Cohen et al (15) reported that dentists and chairside assistants exposed to nitrous oxide had a 1.8-fold to 4.4-fold increase in nonspecific neurological symptoms (tingling, numbness, and muscle weakness) when compared with colleagues without long-term exposure to subanesthetic levels of nitrous oxide. In experimental animals, halothane has been shown to cause damage to the central nervous system at concentrations as low as 8—12 ppm (8, 76). Layzer (57) collected data about 15 cases of nitrous oxide neurotoxicity in the United States. Twelve of these involved dentists who had repeatedly administered nitrous oxide to themselves and who had also been exposed to the gas during their occupational activities. Neurological examinations revealed sensorimotor neuropathy and a picture similar to that of subacute, combined degeneration of the spinal cord (58).

Other health hazards

Anesthetic gases have repeatedly been shown to depress the immune response [for a review, see Graham (36)]. Both nonspecific and specific immune responses can be affected. However, at present, scientists do not sufficiently understand the impact of these effects on health.

Various studies suggest that long-term exposure to nitrous oxide can cause both

impaired metabolism of vitamin B_{12} and the production of tetrahydrofolate (2). These findings may explain a syndrome (which involves early sensory complaints, loss of balance, leg weakness, gait ataxia, impotence, and sphincter disturbances) that develops in individuals exposed to nitrous oxide for long periods of time (57).

Summary and recommendations

Evaluating the risks associated with long-term exposure to low doses of anesthetics is a difficult matter of immediate concern. At present, it can be stated with reasonable conclusiveness that operating room personnel have an increased risk of spontaneous abortion. Furthermore, there is reason to believe that nitrous oxide is the causative factor. This does not mean that other anesthetic agents, eg, halothane, should be regarded without suspicion.

Intermittent exposure to high concentrations of nitrous oxide can apparently induce lesions indicating interference with the metabolism of vitamin B_{12}. The other effects are more controversial. The increased risk of exposed women having malformed children, the increased risk of spontaneous abortion among women whose husbands have been exposed to anesthetic gases, and the chronic effects on the central nervous system, the liver, and the kidneys all need further evidence and support before they can be considered conclusive.

In view of the suggestive evidence of problems associated with long-term exposure to anesthetics, a prudent health policy would be to strive to use the technology currently available for the reduction of occupational exposure to all anesthetic agents.

ANTICANCER CHEMOTHERAPEUTIC DRUGS

Properties and occurrence

Cancer chemotherapy, a relatively new means of treating cancer, came into use around the end of the 1940s, when nitrogen mustard and its derivatives were introduced. The carcinogenicity of HN_2 has been recognized since 1949, the carcinogenicity of triethylenemelamine since 1954, and that of cyclophosphamide since 1966 [see the report of Schmäl (78)]. The possible genotoxic health effects of these drugs and their carcinogenicity, mutagenicity, and teratogenicity have since received increasing attention. During recent years the number of reports on the formation of secondary tumors after cytostatic treatment has increased (1, 39, 71, 80).

Mutagenicity, carcinogenicity and teratogenicity

Rodent carcinogenesis bioassays have provided ample evidence that the alkylating agents, as a class, are potent carcinogens in animals (table 3). In mice and rats, nitrogen mustard, triethylenemelamine, chlorambucil, melphalan, and cyclophosphamide have induced pulmonary tumors and, in some instances, other tumors such as sarcomas, lymphomas, and leukemia. Some antimetabolites are also carcinogenic in animals, although it is not clear whether this carcinogenicity represents a direct oncogenic effect. Thus many of the alkylating agents, many of the antitumor antibiotics, and some of the antitumor antimetabolites are carcinogens in animals. Two synthetic antitumor agents (methylnitrosourea and procarbazine) are also strongly carcinogenic. The case reports and clinical surveys describing the emergence of a second tumor after chemotherapy for an original tumor provide some evidence, albeit circumstantial, that these agents may have similarly carcinogenic effects on man.

Alkylating agents are very reactive towards molecules with negative charges (nucleophiles) such as ionized carboxylic and phosphoric acids and thiols. Alkylating agents are also highly reactive towards molecules with negative areas due to the presence of amine groups. These agents react with many biological constituents, including nucleic acids and proteins.

Amino acid antagonists inhibit the synthesis of protein. A few amino acid antagonists (eg, mercaptopurine, methotrexate, and aminopterin) are both teratogenic and mutagenic. Spindle poisons which are both teratogenic and mutagenic include vinblastine and vincristine.

Anticancer drugs and the liver

The liver plays a prominent role in the metabolic activation and degradation of many antineoplastic agents (table 4). Thus the occurrence of clinical liver disturbances among patients treated with antineoplastic drugs has become an important problem. Simultaneously, increasing emphasis is being placed on the possible hepatic effects of long-term, low-grade occupational exposure among hospital personnel. Ménard et al (63) have recently published a review of the effects of antineoplastic agents on the liver.

Most clinical reports published on the hepatotoxicity of antineoplastic drugs do not even consider all other possible causes of liver toxicity. Therefore the assessment of the hepatotoxicity is necessarily somewhat arbitrary.

Once antineoplastic drugs have shown hepatotoxicity in patients, the medical surveillance of the personnel of anticancer units should be intensified.

Occupational health hazards

The handling of cytostatic drugs by hospital personnel may constitute an occupa-

Table 3. Summary of commonly used anticancer agents with carcinogenic, mutagenic, teratogenic, or immunosuppressive effects.[a] [M = mouse, R = rat, Mk = monkey, Rb = rabbit, H = hamster, BCNU = 1,3-bis(2 chloroethyl)-1-nitrosourea].

Drug class	Carcinogenicity	Mutagenicity		Teratogenicity	Immunosuppressive activity
		Animal	Ames		
Alkylating agents					
BCNU	M	R		R	
Busulfan	M	M		R	+
Chlorambucil	M, R			M, R	+
Cyclophosphamide	M, R	M	+	M, R, Rb	+
Dibromomannitol	M, R				
Nitrogen mustard	M	M	+	M, R	+
Phenylalanine mustard	M, R		+		+
Thiotepa	M	M	+	M, R	
Triethylenemelamine	M, R	M		M, R	+
Cis-diamminedichloroplatinum (II)			+		
Antibiotics					
Actinomycin D	M, R	M	—	R, Rb	+
Adrianmycin	R		+	R	+
Asparaginase					+
Bleomycin			—	R	+
Daunomycin	R		+	R	+
Mithramycin	M, R				—
Mitomycin C	M, R	M			
Streptozotocin				R	
Antimetabolites					
Cytosine arabinoside				R	+
5-Fluorouracil				M, R, Mk	+
6-Mercaptopurine	M, R	M	+	R	+
Methotrexate	M, H		—	R, Mk	+
6-Thioguanine					+
Mitotic inhibitors					
Vincristine				M, R, H, Mk	+
Vinblastine		M		M, R, H, Mk	+
Miscellaneous					
Hydroxyurea	M			R, H, Mk	
DTIC	M, R	M		M, R, Rb	+
Procarbazine	M, R, Mk			R	+

[a] Data summarized from Sieber & Adamson (80), Weisburger et al (91), Harris (40), Adamson & Sieber (1), and Guarino (37).

tional health hazard. One way of assessing the individual's possible exposure to mutagenic or carcinogenic agents is to analyze chromosome damage and sister chromatid exchanges (SCEs) in peripheral blood lymphocytes.

All the drugs which bind to deoxyribonucleic acid (DNA) or give rise to structural DNA damage seem to increase the frequency of SCEs, whereas cytostatic agents interfering with the precursor supply of DNA synthesis have no such effect. A few exceptions to this rule, however, do exist. For instance, actinomycin D and bleomycin either bind to DNA or cause chromosome aberrations in vitro, but they have not been shown to induce SCEs in vivo (55).

Results from several in vitro studies with human lymphocytes suggest that mono- and bifunctional alkylating agents such as mitomycin C, chlorambucil, thiotepa (59), and busulphan (48) cause a marked increase in the frequency of SCEs, but two antimetabolites (methotrexate and cytarabine) and one antitumor antibiotic (bleomycin) have no such effect (59).

Two studies have been performed on hospital personnel who handle cytostatic drugs. In a Finnish study, Norppa et al (70) found an increased frequency of SCEs in the blood lymphocytes of nurses handling cytostatic drugs. The nurses were compared with a group of office workers. The nurses in oncology wards also had a higher frequency of SCEs than other hospital nurses, but this difference was not statistically significant. The frequency of SCEs among patients receiving cytostatic drugs was highly increased. Waksvik et al (89) showed that a group of 11 nurses handling cytostatics in a cancer clinic had a small but significantly increased frequency of SCEs in their peripheral blood lymphocytes when compared with a group of ten female hospital clerks.

The urine of nurses with an increased frequency of SCEs in their lymphocytes also had increased mutagenic activity when compared with office personnel (28).

Table 4. Classification of the antineoplastic agents according to their hepatic disposition and their hepatotoxicity in man (63).

Drug class	Hepatic metabolism	Biliary excretion	Hepatotoxicity
Alkylating agents [a]			
BCNU	+	+	+
CCNU	+	+	—
Methyl-CCNU	+	+	?
Busulfan	+	?	—
Chlorozotocin	?	?	?
Streptozotocin	?	?	+
DTIC	+	—	—
Cyclophosphamide	+	?	—
Antibiotics			
Adriamycin	+	+	—
Asparaginase	?	?	+
Bleomycin	+	—	?
Daunomycin	+	+	—
Mithramycin	?	?	+
Mitomycin C	+	+	?
Rubidazone	+	+	—
Antimetabolites			
Azathioprine	+	—	+
Methotrexate	+	+	+
6-Mercaptopurine	+	—	+
Mitotic inhibitors			
Vincristine	+	+	—
Vinblastine	+	+	—

[a] BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea, CCNU = 1-[2-chloroethyl-3-(4-methylcyclohexyl)]-1-nitrosurea, DTIC = 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide.

Not only SCEs, but also chromosome gaps, have been reported to be more frequent in nurses handling cytostatic drugs than in hospital clerks (89). The chromatid gap in itself may not represent serious chromosome damage, but an increase in the frequency of such gaps indicates exposure to mutagenic agents (7).

All of these findings suggest that handling cytostatic drugs constitutes a possible health hazard. Therefore protective measures should be taken when cytostatic drugs are handled.

Summary and recommendations

Although the clinical toxicity of antineoplastic drugs has been well documented, there is little information about the problems that may arise immediately after such agents are handled. Many of these drugs directly irritate the skin, the eyes, the mucous membranes, and other tissues. If handled without due care, most anticancer drugs can cause toxic or allergic local reactions or both. In addition the risks of carcinogenicity and mutagenicity should always be kept in mind by the personnel who administer these drugs. A sensitive monitoring procedure showed that the concentrated urine of nurses who handle cytostatic drugs had mutagenic activity (28). Two studies reported slightly increased frequencies of SCEs in the lymphocytes of nurses handling cytostatic drugs (70, 89). In light of the present evidence, precautions should be taken when anticancer drugs are handled in hospitals. In general, the staff members of oncology units should avoid direct contact with these drugs by wearing protective gloves and face masks. Fume cabinets should be used when capsules and suspensions are being prepared.

CHEMICAL STERILANTS

Sterilization aims at the total destruction of all forms of microbial life. A number of chemicals have been used for this purpose (eg, ethylene oxide, formaldehyde, propylene oxide, glutaraldehyde, methyl bromide, β-propiolactone, etc). Furthermore, a number of antimicrobial agents that inhibit the growth of bacteria is used in hospitals. One agent that has caused much concern is hexachlorophene.

Ethylene oxide

Properties and occurrence

At room temperature and atmospheric pressure, ethylene oxide is a colorless gas. The mean concentration at which odor can be detected is about 700 ppm (1,260 mg/m³) (10). Ethylene oxide is highly reactive and potentially explosive when heated. So that the risk of explosion can be reduced, ethylene oxide is often mixed with other substances, eg, 12 % ethylene oxide and 88 % halocarbon. Ethylene oxide, a high volume chemical, is used primarily in chemical plants, where it is first produced and then used for intermediates. But ethylene oxide is also used as a chemical sterilant in hospitals (66). Reviews of the health hazards of ethylene oxide have recently been published (24, 67).

Mutagenicity, carcinogenicity and teratogenicity

Ethylene oxide is known to be mutagenic in a number of test systems (24, 66, 67), and it binds covalently to DNA. For this reason the US National Institute for Occupational Safety and Health has concluded that occupational exposure to ethylene oxide may increase the frequency of mutations in an exposed human population (66).

Only recently, a long-term inhalation study of rats was completed. The animals were exposed to ethylene oxide in concentrations of 10, 33 and 100 ppm for 6 h/d, 5 d/week, for about 2 a. At the end of the experiment, the incidence of mononuclear cell leukemia in female rats was dose-related, and it increased linearly with increasing concentrations of exposure. Male rats also had a higher frequency of mononuclear cell leukemia, an earlier outcome, or both. Peritoneal mesothelioma was reported to be treatment-related in male rats exposed to 33 and 100 ppm (81).

By subcutaneously injecting ethylene oxide (weekly dosages of 0.1, 0.3, or 1.0 mg/animal), Dunkelberg (21) obtained sarcomas at the injection site. Sarcomas were not found in the controls.

In 1979 Hogstedt et al (46) reported the results of a retrospective mortality study of workers employed at a Swedish ethylene oxide plant. Nine deaths from cancer were found, whereas 3.4 were expected. With regard to cause-specific mortality, two leukemia deaths were found, versus 0.14 expected. The levels of exposure were estimated to have been 10—50 mg/m³ (6—28 ppm) in the 1950s and 1960s.

In another survey Hogstedt et al (47) reported an investigation of leukemia among workers possibly exposed to ethylene oxide at a Swedish factory where a mixture of 50 % ethylene oxide and 50 % methyl formate had been used since 1968 to sterilize hospital equipment. Between 1972 and 1977, three persons (two women and one man) from a workforce of 230 persons had contracted leukemia (0.2 expected). The 8-h time-weighted average concentration of ethylene oxide in the breathing zone was estimated to have been 20 (SD 10) ppm.

The teratogenic potential of ethylene oxide has been tested in mice (54). The results indicate that ethylene oxide is a teratogen in mice when administered intravenously in a dose of 150 mg/kg each day on days 6—8 of gestation.

Occupational exposure in hospitals

Garry et al (33) studied people working in a hospital sterilization facility. The measured ambient concentration of ethylene oxide in the sterilizer room was 36 ppm. Four exposed persons who reported upper respiratory and neurological symptoms also had significantly increased frequencies of SCEs in their lymphocytes. Similar increases in SCEs have been found by other authors (55, 67). Chromosome aberrations have also been found in persons accidently exposed to high concentrations of ethylene oxide (23).

A recent Swedish study found cytogenetic damage in workers exposed to fairly low concentrations of ethylene oxide (45). Fifteen of 28 exposed persons had never been exposed to ethylene oxide levels exceeding 1 ppm as an 8-h time-weighted average. The other 13 persons had been exposed to somewhat higher levels for up to 2.5 a before the investigation, but however their exposure had never exceeded 5 ppm. The effect of ethylene oxide on the frequency of micronuclei in peripheral lymphocytes was even more pronounced than that of smoking.

Summary and recommendations

Ethylene oxide has caused significant increases in mononuclear cell leukemia in rats. The mutagenicity of ethylene oxide has been demonstrated convincingly. Epidemiologic findings suggest an association between ethylene oxide and leukemia. The causal inference from animal studies is compatible with the excesses of cancer found among workers exposed to ethylene oxide.

On the basis of the presented findings, prudent health policy would require that exposure to ethylene oxide be kept at the lowest possible level.

Formaldehyde

Properties and occurrence

Formaldehyde is a highly reactive, colorless, flammable gas. In hospitals, formaldehyde is used both as a chemical sterilant and as an aqueous solution in pathology laboratories. In some countries, formaldehyde is used in embalming fluids. Outside the hospital environment, formaldehyde has widespread use in the paper industry, in the particle-board and plywood industry, etc (68).

The toxicity of formaldehyde has been reviewed recently (25, 26, 68).

Mutagenicity, carcinogenicity and teratogenicity

Formaldehyde is mutagenic to bacteria yeast and to the fruit fly (27). It induces SCEs in Chinese hamster ovary cells and in cultures of peripheral human lymphocytes. Chromosome aberrations have been found in mammalian cells, in plants, and in the spermatocytes of both grasshoppers and fruit flies which have been tested with formaldehyde.

Animal carcinogenicity studies. The Chemical Industry Institute of Toxicology sponsored a study, conducted by Battelle

Columbus Laboratories, which was the first to show evidence for the carcinogenicity of formaldehyde. After 24 months of exposure to 15 ppm of formaldehyde, 93 of 240 rats developed squamous cell carcinomas of the nasal turbinates. Two rats exposed to 6 ppm and two mice exposed to 15 ppm of formaldehyde also developed squamous cell carcinomas of the nasal turbinates (67).

Studies done at the New York University Medical Center confirm the findings of the Chemical Industry Institute of Toxicology. In these studies, hydrochloric acid, also a potent irritant, was used as the exposing agent. Hydrochloric acid alone did not produce cancer (86).

Epidemiologic studies. Three cases of cancer in the nasal cavities, the sinuses, or the nasopharynx were reported among Danish doctors during the period 1943—1976 (49). None of them had worked in a pathology department.

In the United States excess primary liver cancer and lung cancer have been reported among pathologists when compared with radiologists (60). There is no way of connecting these cancers causally to formaldehyde exposure.

In summary, the existing epidemiologic studies are inadequate to provide any evidence for the possible carcinogenicity of formaldehyde in humans.

Other health effects

The acute effects of formaldehyde in man have been well documented (69). Irritation of the eyes, the nose, and the throat is associated with exposure to formaldehyde. Such irritation can lead to lacrimation, sneezing, shortness of breath, sleeplessness, a tight chest, nausea, and excess phlegm. Most people experience irritation of the eyes, the nose, and the throat when 0.1—3 ppm of formaldehyde is present in the air.

Five nurses working near an artificial kidney (hemodialysis) machine developed wheezing and recurrent episodes of cough (12). The formaldehyde used to sterilize the machine was reported to have caused this respiratory distress.

Dermatitis caused by formaldehyde solutions is a well known problem (34, 75).

Summary and recommendations

Formaldehyde can cause DNA damage in bacteria, yeast, and mammalian cells. It is mutagenic in many test systems. Formaldehyde has induced a rare form of cancer in rats and mice, as reported by the Chemical Industry Institute of Toxicology and by the New York University Medical Center. In spite of inadequate epidemiologic findings, evidence of its genotoxicity and carcinogenicity in animals makes it likely that formaldehyde is also a human carcinogen. For this reason formaldehyde should be handled in the workplace as a potential occupational carcinogen. The US National Institute for Occupational Safety and Health has published guidelines for minimizing employee exposure to formaldehyde (67).

Other antimicrobial agents

Hexachlorophene (2,2'-methylenebis [3,4,6-trichlorophenol]) has been used extensively as an antibacterial and antifungal agent.

Hexacholorophene can penetrate both the skin and the placental barrier. A local application of hexachlorophene to the skin can cause neurotoxicity in animals (73, 85). Both positive and negative studies have been published on the teratogenicity of hexachlorophene in experimental animals [see Halling (38)].

Metabolites of hexachlorophene can bind covalently to cellular macromolecules (64).

Retrospective epidemiologic studies carried out in six Swedish hospitals have raised concern about congenital malformations in neonates born to women who used hexachlorophene soaps in hospitals (frequent handwashings together with the extensive use of hand creams) (38). Halling's original findings prompted a subsequent study of the outcome of pregnancy in hospital personnel by the National Board of Health and Welfare in Sweden. In this study the perinatal death rates and malformation in the children of hospital personnel were surveyed during 1973—1975. No significant differences were found, except for an excess of perinatal deaths among the children of hospital personnel in 1973 only (4). A case-referent study of 340 children born with oral clefts in Finland revealed no excess exposure to

hexachlorophenol among the case mothers (43). Thus the nature and the level of the potential risk linked to the use of hexachlorophene is still unclear.

Sodium o-phenylphenate, a fungicide and antimicrobial agent used, eg, in many hospital soaps, has recently been shown to cause tumors in the urinary tract of rats (44).

Propylene oxide has been found mutagenic in *Neurospora, Drosophila,* and *Salmonella typhimurium* bacteria (72). Propylene oxide has also been shown to be a carcinogen (21, 90).

DISCUSSION

Existing knowledge on occupational hazards in hospitals has traditionally been more concerned with such conditions as ionizing radiation or potentially life-threatening diseases, eg, hepatitis B, than with chemical hazards. However, occupational skin diseases are certainly of importance in hospitals, due to the use of chemicals with irritant properties (such as disinfectants and detergents) or due to the allergic dermatoses arising from certain metals, aldehydes, antibiotics, or rubber products. In addition to the use of reactive chemicals in disinfection and cleaning processes, potent biologically active chemicals are being used in cancer chemotherapy. The use of anticancer drugs in cancer chemotherapy is for the benefit of the patients, and, in the same context, care should be taken not to have any unnecessary exposure of the hospital staff, the agents also having mutagenic, teratogenic, and cancer-causing properties.

Women form a large proportion of hospital employees in all countries. Pregnancy outcome studies have been frequently done among operating room personnel in many countries. However, such studies are almost nonexistent among other occupational groups in hospitals. As concluded also by a recent working group of the World Health Organization (92), pregnancy outcome studies of employees in areas such as oncology units or those exposed to chemical sterilants should be encouraged.

Although chemical hazards within hospitals are legion, epidemiologic studies showing risks are infrequent. This lack may be due to the nonexistence of real risks or to the fact that studies simply have not been performed or to the wide use of chemicals having begun only in the late 1960s. The most prominent effects of occupational chemical exposures detected so far have been dermatologic problems and spontaneous abortions among operating room personnel. In addition to the chemical risks dealt with in this review, there are many other potential chemical hazards related to, eg, the use of plastic biomaterials (19, 39, 62, 74). While the well-established infection diseases must not be forgotten, more emphasis should be placed in the future on the possible chemical hazards in hospitals.

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